A Pilot Study of Online Yoga to Improve Fatigue and Quality of Life in Myeloproliferative Neoplasm Patients

by

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A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved June 2017 by the
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August 2017

ABSTRACT

Myeloproliferative neoplasm (MPN) patients suffer from fatigue and a reduced overall quality of life, both of which are not resolved with current pharmacologic therapy. The purpose of this study was to examine the effects of a 12-week online-streamed yoga intervention on fatigue and QoL in MPN patients as compared to a wait-list control group as well as to determine the feasibility of remotely collecting blood and saliva samples in a national sample. MPN patients were asked to complete 60 min/week of online yoga for 12 weeks. MPN fatigue and QoL were assessed online with single-item questions taken from the MPN SAF (fatigue and QoL) and NIH PROMIS (QoL) at baseline, week 7, and week 12. The practicality of the blood and saliva measures were defined as >70% completion rate at both baseline and week 12. Fidelity of the intervention (i.e., weekly yoga participation) was assessed via both self-report (i.e., daily log) and objective measurement (i.e., Clicky). Of the 62 MPN patients that enrolled in the study, 48 completed the intervention with 27 participating in the yoga group and 21 participating in the wait-list control group. Weekly yoga participation averaged ~41 min/week as measured objectively, whereas self-report yoga participation averaged ~56 min/week. The blood draw was determined to be practical with a 92.6% completion rate at baseline and a 70.4% completion rate at week 12. There were no significant differences from baseline to week 12 in MPN SAF fatigue (ES=0.18; p=0.724) or MPN SAF QoL (ES=-0.53; p=0.19), however, NIH PROMIS QoL was significantly improved from baseline to week 12 (ES=0.7; p=0.031) when compared to the control group. This study builds upon the findings from a prior feasibility study in demonstrating the feasibility of online yoga as well as its preliminary effects of improving total symptom burden, fatigue, pain,

depression, anxiety, and sleep disturbance in MPN patients. Given the effects of yoga demonstrated both in the feasibility study and the current pilot study, a future randomized controlled trial with a larger sample size is warranted in order to further investigate the effectiveness of online yoga for MPN patient symptom burden and QoL.

ACKNOWLEDGMENTS

I would like to acknowledge the hard work and dedication to my academic success of my Thesis committee members, including Dr. Krisstina Gowin, Dr. Ruben Mesa, Dr. Amylou Dueck, Heidi Kosiorek, Dr. Linda Larkey, and Dr. Jennifer Huberty. This Thesis project would not have been possible without my committee's guidance and expertise. I am truly thankful for all of their work in helping me succeed. Additionally, I am grateful to all of the study participants that dedicated their time, energy, and effort into this study. Finally, I would like to acknowledge friends, co-workers, and family that have helped me along this journey with their support and encouragement. Accomplishments such as this are never achieved in isolation and to have an amazing group of individuals to support me has been instrumental in my success.

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INTRODUCTION

In 2014, there were an estimated 1,665,540 new cancer cases and 585,720 cancer deaths in the United States.[1,2] Hematological cancers, while less prevalent than some of the more common types of cancers (i.e., breast, prostate, lung & bronchus, colorectal), accounted for 9.4% of all cancers diagnosed as well as 3.3% of all cancer deaths in the United States in 2014.[3] Hematological cancers represent a heterogeneous group of blood- and lymph-related disorders, including leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), myelodysplastic syndromes (MDS), myeloma, and myeloproliferative neoplasms (MPNs).[3]

Compared to other hematological cancers, MPNs are relatively new, being first recognized in 1951 by William Dameshek as "myeloproliferative disorders."[4] The "classic" Philadelphia-negative myeloproliferative neoplasms, as they are now referred to, include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Each is characterized by mutually exclusive Janus Kinase 2 (*JAK2*), calreticulin (*CALR*), and myeloproliferative leukemia oncogene virus (*MPL*) mutations. *JAK2* mutation is the most frequently occurring gene mutation, occurring in approximately 98% of PV cases, 50-60% of ET cases, and 55-65% of PMF cases.[5] Due to differences in the etiology between MPN sub-types, symptom profiles can vary greatly. Typical symptoms, however, include (but are not limited to) fatigue, pruritus, loss of appetite, night sweats, splenomegaly, abdominal pain, bone pain, weight loss, microvascular complications, and anemia.[6,7]

Fatigue is the most commonly reported symptom among MPN patients. In a survey of 1179 MPN patients, fatigue was reported by 81% of patients.[6] In separate

surveys, fatigue has been reported by as many as 92.7% of patients.[8] Other commonly reported symptoms include insomnia (65.4%), sad mood (62.7%), early satiety (61.9%), concentration difficulties (61.7%), numbness (61.3%), inactivity (60.5%), sexual problems (57.9%), dizziness (55.2%), and pruritus (52.6%).[8]

The symptom burden of MPNs often leads to a reduced overall quality of life (QoL), including a reduced ability to participate in physical and social functions as well as a reduced capacity to complete activities of daily living.[6] As many as 84% of MPN patients report an impaired QoL, which has been defined as a score of >0 (0-10 scale) on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN SAF).[6]

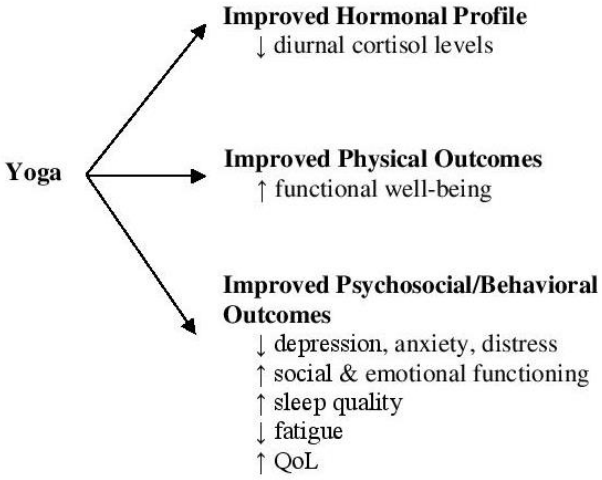
Treatment for MPNs primarily focuses on managing disease progression as well as maintaining or improving QoL and reducing symptom burden. To date, pharmacologic approaches have been the mainstay of treatment options for the MPN patient population. Typical treatment options for this population may include, but are not limited to, pharmacotherapy (e.g., aspirin, hydroxyurea, interferon, cytoreduction, androgens, corticosteroids, erythropoiesis-stimulating agents, radioactive phosphorus (P3-32), and Janus Kinase (JAK) inhibitors), radiation therapy (e.g., splenic irradiation), surgery (e.g., splenectomy), or stem-cell transplantation.[7,9]

Allogenic stem-cell transplantation is the only curative therapy for MPN patients, but is utilized very infrequently and is reserved for those afflicted with intermediate- to high-risk PMF. Given the lack of curative therapies for the treatment of MPNs, patients often live with a significant symptom burden for the rest of their life. Current pharmacologic approaches, specifically JAK-inhibitors, have demonstrated some success in improving symptom burden and overall QoL in MPN patients;[7,10] however, these

treatment modalities often come with side effects (e.g., anemia, thrombocytopenia). For example, Ruxolitinib (selective JAK-inhibitor) has demonstrated efficacy in clinical trials for improving MPN-related symptoms (e.g., fatigue, inactivity, night sweats, muscle/bone pain, pruritus, early satiety, dyspnea, and abdominal discomfort) and QoL as well as reducing splenomegaly;[11-16] however, anemia and thrombocytopenia are common side effects of this particular treatment.[7,10] Additionally, MPN patients that do respond to treatment are often left with unresolved fatigue, depressive symptoms, and insomnia.[17,18] Thus, there is a need to explore other approaches (without side effects) to manage symptom burden and QoL in MPN patients.

Yoga, which consists of physical postures (asanas) and mindfulness-based techniques (e.g., focus on breath, meditation, etc.) has been an effective approach to improve a variety of physical and psychosocial outcomes in other cancers (see Figure 1). Systematic reviews and meta-analyses have found that yoga significantly improves functional well-being, distress, anxiety, depression, fatigue, emotional function, social function, sleep quality and QoL.[19-21] Additionally, some studies have demonstrated a possible association between decreases in cortisol and improvements in psychosocial outcomes in cancer

Figure 1. Effects of Yoga on Cancer Patients



patients.[22,23] Vadiraja et al.[23] demonstrated that mean diurnal cortisol levels decreased significantly ($p<0.05$; ES=0.27) along with significant improvements in anxiety ($p<0.001$), depression ($p<0.01$), and perceived stress ($p<0.001$) in breast cancer patients (n=88) participating in a 6-week, 3x/week yoga intervention. Much of the aforementioned work, however, has been done in breast cancer patients.

Minimal research to date has examined the effects of yoga on MPN patient outcomes. There is non-experimental data indicating that MPN patients are interested in yoga as a symptom management strategy, particularly for fatigue. In a survey of 1788 MPN patients, 73% reported attempting to exercise (43% of those attempted yoga) in order to self-manage fatigue, with 63% of these patients reporting exercise as a successful strategy.[24] This data is cross-sectional, however, and requires further experimental investigation in order to identify physical activity, including yoga, as an effective symptom management (i.e., fatigue) for the MPN patient population.

Our prior work lends support to the previous cross-sectional data.[25] We conducted a 12-week feasibility of a home-based, online streamed yoga intervention in MPN patients (n=38). Online yoga was reported to be feasible as average yoga participation was ~50 min/week (60 min/week was prescribed) and 37% averaged ≥60 min/week of yoga. Furthermore, 68% were satisfied with the intervention and 75% felt that it was helpful for dealing with MPN-related symptoms. This study also provided preliminary evidence to support the role of yoga for improving MPN symptom burden and QoL outcomes as significant differences between pre- and post-intervention were seen in patient-reported total symptom burden ($p=0.004$; ES=-0.36), fatigue ($p=0.04$; ES=-0.33),

anxiety ($p=0.002$; ES=-0.67), depression ($p=0.049$; ES=-0.41), and sleep ($p<0.0001$; ES=-0.58).

Although there are a few studies related to yoga and MPN patients, only one study provides experimental support for yoga. This study was conducted to determine the feasibility of online yoga as its primary outcome[25] and did not include a control group and, therefore, the significant findings are preliminary in nature. Due to the limited research investigating the role of yoga in MPN patients as a non-pharmacological symptom management approach, a review of the literature as it relates to yoga in other hematological cancers will be discussed in the following section.

LITERATURE REVIEW

Literature Review Methods

The review was conducted by performing selective inclusion of studies investigating yoga (defined as the combination of physical postures and mindfulness techniques) in specific hematological cancer sub-types (see Table 1). Studies that

Table 1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
- Published study between 1995-2016 - Examined any type of yoga as an either an independent variable or a dependent variable - Included leukemia, lymphoma, and/or myeloma patients or survivors as study participants - Intervention or epidemiological study design	- Study participants included patient population receiving stem-cell transplantation - Examines yoga in relation to hematological cancer risk - Systematic review or meta-analysis study design

examined yoga as an independent variable or a dependent variable were included as were intervention (e.g., RCT, quasi-experimental) or epidemiological (e.g., longitudinal, cross-sectional) study designs. However, systematic reviews and meta-analyses as well as studies that examined yoga in relation to hematological cancer risk were excluded as this review intended to focus on primary research examining yoga and its effects on hematological cancer patient symptom burden and QoL. Additionally, studies including a patient population that underwent stem-cell transplantation were excluded, as this patient population may present with complications and issues that aren't transferrable to the general MPN patient population. Stem-cell transplantation may result in acute and chronic complications, such as reduced immune function, prolonged neutropenia,

infectious complications, veno-occlusive liver disease, and graft-vs-host disease,[26] that aren't typically present in the general MPN patient population as this type of surgery is usually reserved for high-risk PMF patients. A medical librarian developed search strategies for Ovid MEDLINE, Ovid Embase, and PubMed in order to identify articles. The search strategies were peer-reviewed by another experienced medical librarian. Limitations included a publication date range of 1995 to 2015. Search strategies included the MeSH terms and key words below (see table 2). A total of one article was included for review and is summarized in Table 3.

Table 2. Keyword Search Terms

MeSH Terms (PubMed)	Keywords (PubMed)
yoga	yoga
hematologic neoplasms	multiple myeloma
multiple myeloma	leukemia
leukemia	lymphoma
lymphoma	
Myeloproliferative disorders	

Literature Review

Table 3. Summary of Included Articles

Reference	Study Design	Study Sample	Exercise Prescription	Significant Findings	Limitations
Cohen et al., 2001	RCT (wait-list control group)	Lymphoma patients (n=39; *20 in intervention*)	7 weeks; 1x/week; light-intensity; unknown session duration; Tibetan yoga	89% completed 2-3 sessions; 57% completed ≥ 5 sessions; ↓sleep disturbance; ↑sleep quality; faster sleep latency; ↓use of sleep meds	Low overall exercise dose; small sample size in intervention group (n=20); yoga session duration not specified

The only article included in this review consists of a study conducted by Cohen et al.[27] Lymphoma patients (n=39) were randomized to participate in a yoga intervention (n=20) or a wait-list control group (n=19). The intervention group performed Tibetan yoga (e.g., breathing, visualization, mindfulness, and low-impact postures) 1x/week for seven weeks (duration of each session was not specified). The primary outcomes for this study included sleep quality measures (i.e., overall quality, latency, duration, sleep medication use), state anxiety, depression, and fatigue. Although significant improvements in subjective sleep quality, faster sleep latency, longer sleep duration, and less reported use of sleep medications were found, there were no significant differences between groups for state anxiety, depression or fatigue. However, this may be due, in part, to both the adherence rate and the dose of the intervention. Only 58% of patients in the intervention group completed at least 5 yoga session (out of 7 total sessions). Additionally, seven total sessions may not have been a potent enough stimulus to improve psychosocial outcomes (i.e., anxiety, depression, and fatigue) as previous yoga studies demonstrating significant improvements in anxiety, depression, and fatigue in breast cancer patients have used higher doses (i.e., 18-24, 60-minute sessions).[23,28,29] Yoga interventions with doses greater than seven total sessions should be investigated in lymphoma patients.

STUDY PURPOSE & HYPOTHESES

As demonstrated in the literature review, there is only one study providing preliminary support for yoga in hematological cancer patients. With much of the work being done in breast cancer patients, there is a strong need for future research examining the effects of yoga on MPN patient symptom burden and QoL. Eckert et al.[30] has suggested in a recent review of the literature that, because of the success of physical activity interventions in other hematological cancer patients, the feasibility and effectiveness of physical activity interventions (including yoga) in MPN patients should be explored. Huberty et al.[25] has successfully conducted a feasibility study investigating the effects of online-streamed yoga in MPN patients and has preliminary findings that demonstrate improvements in patient-reported fatigue and QoL-related outcomes. Therefore, the primary purpose of this study is to implement a pilot study further examining the effects of online-streamed yoga for fatigue and QoL in MPN patients as compared to a control group. Secondarily, the feasibility of collecting blood and salivary biomarkers that may be associated with fatigue will be investigated.

Specific aim 1: To investigate the efficacy of online streaming yoga to reduce fatigue and improve QoL as compared to a wait-list control group in MPN patients.

Hypothesis 1: Online streaming yoga will significantly improve patient-reported fatigue and QoL in MPN patients as compared to a wait-list control group.

Specific aim 2: To explore the feasibility (i.e., implementation and practicality) of collecting blood (i.e., serum cytokines) and salivary (i.e., cortisol) biomarkers that may be associated with fatigue in MPN patients participating in an online yoga intervention.

Hypothesis 2: Blood (i.e., serum cytokines) and salivary (i.e., cortisol) biomarkers that may be associated with fatigue will be feasible (i.e., successfully implemented and practical) to collect in MPN patients participating in an online yoga intervention.

METHODS

This study was approved by the Institutional Review Board at Arizona State University. All study participants completed an informed consent prior to participating.

Study Participants

Participants for the study included MPN patients with the following: 1) a diagnosis of essential thrombocythemia (ET), polycythemia vera (PV), or primary myelofibrosis (PMF) identified by a treating physician, 2) answered "no" to all items on the Physical Activity Readiness Questionnaire (PAR-Q) or be willing to obtain a signed medical release from their physician, 3) had access to a desktop or laptop on a regular basis, 4) had access to reliable internet, 5) been able to read and understand English, 6) were 18 years or older, 7) were willing to be randomized to a yoga group or a wait-list control group, and 8) were willing to drive to the nearest Patient Service Center to have their blood drawn. Potential participants were excluded if they: 1) currently performed Tai Chi, Qi Gong, or Yoga at least 60 minutes or more weekly, 2) currently participated in ≥150 minutes/week of physical activity, 3) currently utilized Udaya.com, 4) had a history of syncope in last 2 months, 5) had a history of recurrent falls (≥2 in 2 months), 6) had a score of ≥15 on the Patient Health Questionnaire (PHQ-9) indicating moderate-severe clinical levels of depression, and 7) had an Eastern Cooperative Oncology Group 3 (ECOG 3) score greater than three, 8) were currently pregnant, or 9) were currently residing outside of the United states of America. Table 4 describes the inclusion/exclusion criteria.

Table 4. Participant Inclusion/Exclusion Criteria	
Inclusion Criteria	**Exclusion Criteria**
- Diagnosis of ET, PV, or PMF - Answer "no" to all items on PAR-Q or be willing to obtain medical release - Access to desktop or laptop on a regular basis - Access to reliable internet - Able to read and understand English - ≥18 years of age - Willing to be randomized to yoga group or wait-list control group - Willing to drive to the nearest Patient Service Center for blood draw	- Currently perform Tai Chi, Qi Gong, or Yoga for ≥60 min/week - Currently engage in ≥150 min/week of physical activity - Currently utilize Udaya.com - History of syncope in last 2 months - History of recurrent falls (≥2 in 2 months) - Score of ≥15 on PHQ-9 indicating moderate/sever levels of depression - ECOG 3 score >3 - Currently pregnant - Currently residing outside of the United States of America

Recruitment

MPN patients were recruited nationally utilizing internet-based strategies, including social media (i.e., Facebook, Twitter), social networking sites, online and email listervs, and by contacting MPN patients that were not included in our prior feasibility study but expressed their interest in our future research. Prospective organizations were contacted via email and/or phone and asked to advertise the study by posting the provided recruitment material (i.e., flyers, blurbs) to their website or social media site. Those MPN patients that expressed interest in future studies were emailed and asked of their interest in the current study. Interested participants were then directed to an eligibility survey administered via Qualtrics (Provo, Utah).

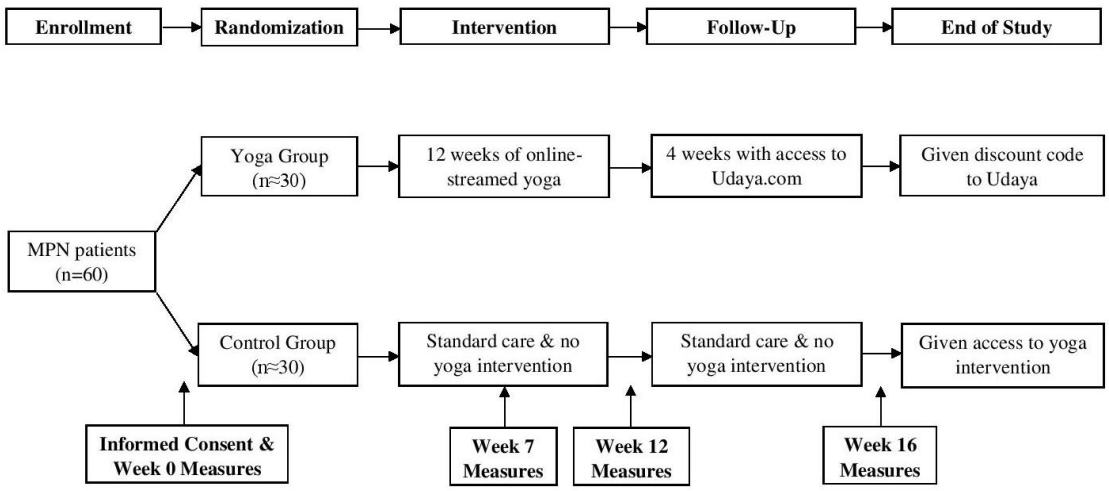
Research Design

The study was a randomized controlled trial study design. Sixty MPN patients were randomized, after consenting, to either a yoga group (n=~30) or a standard care, wait-list control group (n=~30). Participants randomized to the yoga group were asked to complete 12 weeks of at least 60 min/week of online-streamed, home-based yoga through Udaya.com (Udaya inc.). Those randomized to the wait-list control group were asked to resume their normal levels of physical activity for 16 weeks before being given access to the online yoga intervention materials (see Figure 2). The following sections describe the study-related procedures for the yoga group and the wait-list control group, respectively.

Yoga Group

The 12-week yoga prescription was a modified version of the yoga prescription from the previous feasibility study conducted by Huberty et al.[31] The yoga prescription used in the feasibility study was designed to be safe and progressive for cancer patients and was approved by physicians on staff. Overall, the yoga prescription was 12-weeks and included 20-30 minute videos on 2-3x/week to achieve 60 minutes of yoga

Figure 2. Study Design Flow Chart



participation each week. Weeks 1-2 were designed to be introductory in nature, with short class video lengths (i.e., 5-20 minutes). Class length and difficulty gradually progressed thereafter in weeks 3-12 to include longer and slightly more challenging videos (i.e., 20-30 minutes). Modifications to the yoga prescription used in the feasibility study included the addition of more meditation-based classes. These modifications were made based on qualitative feedback from the feasibility study, in which many participants mentioned that they wished there would have been more options for meditation classes. All study participants were provided with a yoga safety and modifications handout that they were asked to review prior to participating in yoga. Additionally, participants were reminded each week in a weekly email to participate in at least 60 minutes of yoga.

Yoga group study participants were asked to receive a blood draw from a certified phlebotomist at a nearby Patient Service Center (PCS) at both baseline (week 0) and post-intervention (week 12) in order to measure specific serum cytokines (i.e., IL-6 and TNF-a) as well as complete blood count (CBC). They were also asked to provide saliva samples at both baseline (week 0) and post-intervention (week 12) to assess salivary cortisol. This measurement consisted of providing saliva samples at four different time points (i.e., upon waking, 30 min after waking, noon, and 30 min before bed) over the course of one day. Yoga group participants were incentivized with $10 for completing their baseline blood draw and $20 for completing their post-intervention blood draw.

Yoga group participants were also asked to complete weekly self-report logs (i.e., daily yoga logs) detailing the amount of time spent participating in yoga. Objective yoga participation was assessed using Clicky (i.e., web analytics program) and by gathering the amount of time (i.e., minutes) spent viewing yoga videos. Questionnaires were

administered at 4 time points throughout the study, including baseline (week 0), mid-point (week 7), post-intervention (week 12), and follow-up (week 16). These questionnaires included questions pertaining to patient demographics, MPN-related health history information, study satisfaction, and both fatigue and QoL via the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF). Yoga group participants were incentivized with $20 for completing all four questionnaires.

Control Group

Control group participants were not asked to receive blood draws or to provide saliva samples. Those in the control group were only asked to complete the 4 questionnaires (baseline, mid-point, post- and follow-up). The questionnaires were identical to the questionnaires given to the yoga group, with the exception of any study satisfaction-related questions. Control group participants were also incentivized with $20 for completing all four questionnaires. Upon completing the 4-week follow-up questionnaire, control group participants were provided with the same instructions that the yoga group received so that they could participate in 12-weeks of online yoga. There were no further measures for the control group to complete beyond week 16, however research staff was still available via email/phone if participants in the control group had questions related to the yoga prescription.

Independent and Dependent Variables

The independent variable in the proposed study was yoga. The dependent variables were fatigue, QoL, and feasibility of the blood draw. The yoga intervention was delivered over 12-weeks, was home-based, and streamed online. To answer the proposed hypotheses, fatigue was measured directly with a single question in the MPN SAF. QoL

outcomes included a single QoL question within the MPN SAF as well as a single question from the NIH PROMIS-10 Global Health measure. Self-reported raw scores were used for both the MPN SAF and NIH PROMIS-10 Global Health QoL measure. The feasibility of the blood draw and saliva sample collection was assessed through its practicality as described by Bowen et al.[32] Practicality was defined as >70% of study participants completing both the pre- and post-intervention blood draw and saliva sample measures.

Statistical Analyses

Data collected from questionnaires and blood draws were entered into the Statistical Package for Social Sciences (SPSS) version 24.0 (Armonk, NY). Descriptive statistics (e.g., mean standard deviation, and frequencies) were calculated for both continuous and categorical variables with 95% confidence intervals. The Shapiro-Wilk test was used to check for normality with continuous variables because the expected sample size is <50. A p-value >0.05 signifies normally distributed data. All non-normal data was transformed to achieve normal distribution. Analysis of covariance (ANCOVA) was used to determine differences in outcome variables (i.e., fatigue, QoL measures) at week 7 and 12 between the yoga group and the control group, using the respective baseline score as a covariate. Cohen's *d* was used to determine effect size values. Values of 0.2, 0.5, and 0.8 indicate small, moderate, and large effect size, respectively. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Participant Enrollment

A total of 260 MPN patients completed the eligibility questionnaire, of which 37% n=96) were eligible and the remaining 63% (n=164) were ineligible. Of those that were ineligible, the most common reasons were 1) currently physically active (49.3%; n=81), 2) score of ≥ 15 on PHQ-9 indicating moderate-severe depression (37.2%; n=61), and 3) currently engage in mindful activity of ≥ 60 min/week (26.2%; n=43) (see figure 3). Those that were eligible for this study were emailed to schedule an intake appointment in the order in which they completed the eligibility questionnaire until ~60 participants were enrolled in the study. Of the 96 that were eligible to participate, 62 were enrolled into the study with 34 randomized to the yoga group and 28 to the control group. A total of 48 participants completed all study-related procedures (i.e., completers), with 27 yoga group participants and 21 control group participants completing the intervention. Of those that did not complete the intervention (i.e., dropouts; n=14), 50% (n=7) never responded after completing the informed consent, 28.6% (n=4) discontinued the intervention due to a personal issue not related to the study, and 21.4% (n=3) discontinued the intervention due to concerns with wearing the Fitbit device (i.e., too burdensome). Figure 3 describes study participant enrollment.

Participant Demographics

Table 5 describes participant demographics at baseline. Of the 48 participants that completed the intervention, mean (SD) age was 56.9±10.3 years and mean (SD) BMI was 26.5±5.4 ml/kg^2. The majority of participants were female (n=45), Caucasian (n=45), educated

Figure 3. Enrollment

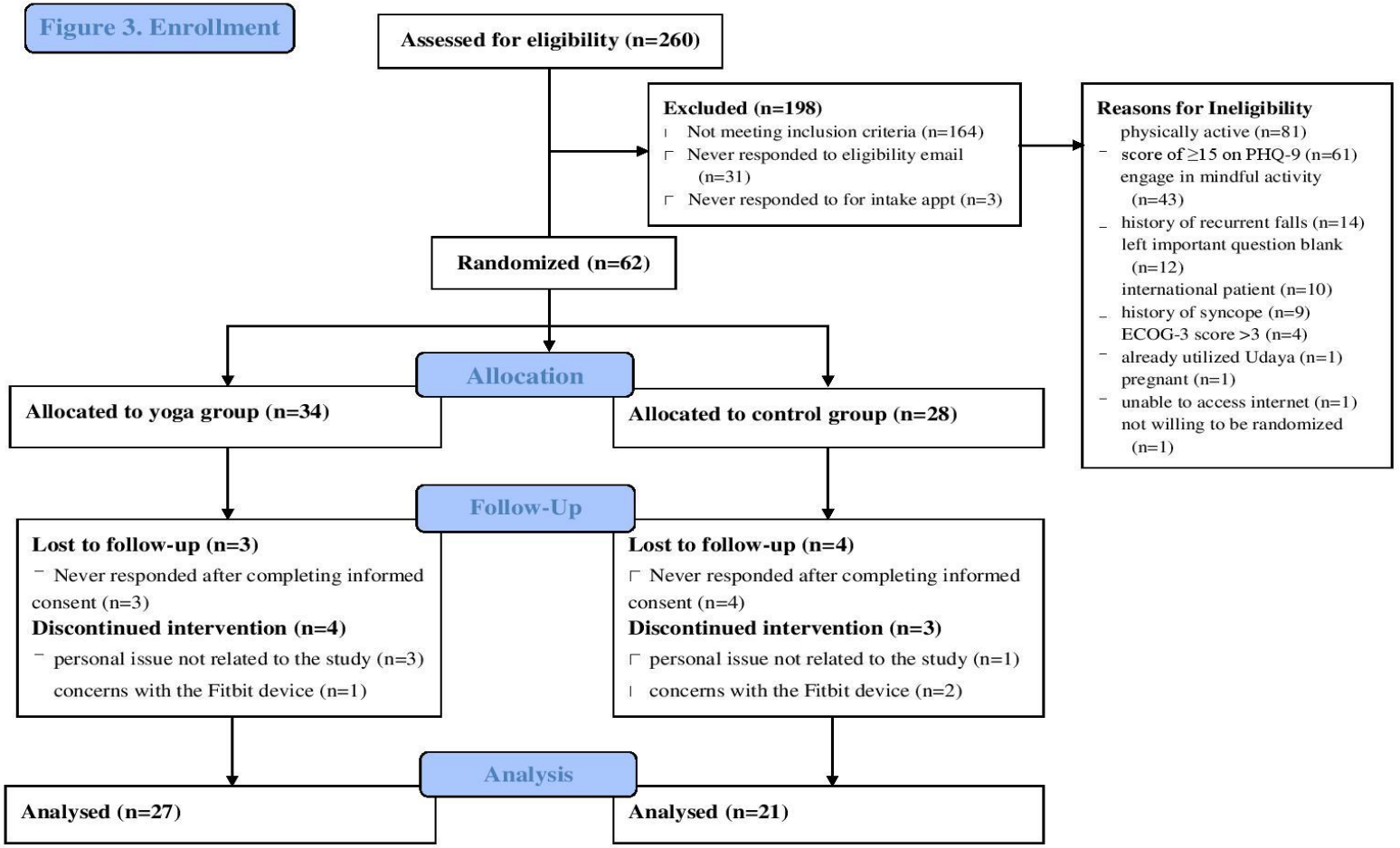


Table 5. Baseline Demographics

	Yoga Group (n=27)	Control Group (n=21)	Total (n=48)	
	N (%)	N (%)	N (%)	p
Age, years (M±SD)	58.3±9.3	55.0±11.4	56.9±10.3	0.28
BMI (M±SD)	26.6±5.4	26.2±5.6	26.5±5.4	0.81
Gender				0.71
Male	2 (7.4)	1 (4.8)	3 (6.3)	
Female	25 (92.6)	20 (95.2)	45 (93.8)	
Race				0.42
Caucasian	25 (92.6)	20 (95.2)	45 (93.8)	
Other	2 (7.4)	1 (4.8)	3 (6.3)	
Diagnosis				0.53
Polycythemia Vera (PV)	10 (37.0)	5 (23.8)	15 (31.3)	
Essential Thrombocythemia (ET)	9 (33.3)	10 (47.6)	19 (39.6)	
Myelofibrosis (MF)	8 (29.6)	6 (28.6)	14 (29.2)	
Time Since Diagnosis				0.44
< 1 year ago	3 (11.1)	4 (19.0)	7 (14.6)	
1-3 years ago	4 (14.8)	4 (19.0)	8 (16.7)	
> 3 years ago	20 (74.1)	13 (61.9)	33 (68.8)	
Presence of Enlarged Spleen				0.45
Yes	8 (29.6)	9 (42.9)	17 (35.4)	
No	17 (63.0)	12 (57.1)	29 (60.4)	
Missing	2 (7.4)	0 (0.0)	2 (4.2)	
History of Anemia				0.23
Yes	15 (55.6)	8 (38.1)	23 (47.9)	
No	12 (44.4)	13 (61.9)	25 (52.1)	
Ruxolitinib/Other JAK-Inhibitor Treatment				0.65
Yes	5 (18.5)	5 (23.8)	10 (20.8)	
No	22 (81.5)	16 (76.2)	38 (79.2)	
Education				0.3
< High School	0 (0.0)	0 (0.0)	0 (0.0)	
High school diploma	2 (7.4)	0 (0.0)	2 (4.2)	
Some college	1 (3.7)	2 (9.5)	3 (6.3)	
Associates/2-year degree	3 (11.1)	0 (0.0	3 (6.3)	
Bachelors degree	10 (37.0)	8 (38.1)	18 (37.5)	
Graduate school or above	11 (40.7)	11 (52.4)	22 (45.8)	
Marital status				0.28
Single	2 (7.4)	0 (0.0)	2 (4.2)	
Partnered/in a relationship	1 (3.7)	2 (9.5)	3 (6.3)	
Married	22 (81.5)	19 (90.5)	41 (85.4)	
Separated	2 (7.4)	0 (0.0)	2 (4.2)	
Divorced	0 (0.0)	0 (0.0)	0 (0.0)	
MPN SAF Fatigue* (M±SD)	5.4±2.3	4.5±2.8	5.0±2.5	0.23
MPN SAF QoL** (M±SD)	6.2±1.7	6.9±2.0	6.5±1.9	0.26
NIH PROMIS QoL*** (M±SD)	3.1±0.8	2.6±0.9	2.9±0.9	0.25

*Fatigue was a single question on the MPN-SAF with a possible score of 0-10; a higher score represents greater fatigue

**MPN SAF QoL was a single question on the MPN-SAF with a possible score of 1-10; a higher score represents greater QoL

***NIH Global Health QoL was a single question on the NIH Global Health Scale with a possible score of 1-5; a lower score represents greater QoL

with Bachelor's degree or higher (n=40), and married (n=41). ET was the most common diagnosis (n=19) followed by PV (n=15) and MF (n=14). The majority of participants were diagnosed with their MPN >3 years ago (n=33), did not have an enlarged spleen (n=29) and were not being treated with a JAK-Inhibitor (n=38). There were no significant differences in any demographic variables between groups (i.e., yoga vs. control). For all study participants, mean (SD) fatigue (MPN SAF) was reported as 5.0±2.5, mean (SD) QoL (MPN SAF) was reported as 6.5±1.9, and mean (SD) QoL (NIH Global Health) was reported as 2.9±0.9.

Blood Draw and Salivary Cortisol Feasibility

Practicality: At pre-intervention, 92.6% (n=25/27) of yoga group participants completed the blood draw and 93.3% (n=14/15 that were eligible) completed the salivary cortisol measure. At post-intervention, 70.4% (n=19/27) completed the blood draw and 60% (n=9/15 that were eligible) completed the salivary cortisol measure.

Yoga Participation

Over the course of the 12-week yoga intervention, objective yoga participation (i.e., Clicky) averaged 40.8 min/week with approximately 15% (n=4/27) averaged ≥60 min/week. There was a decrease in weekly yoga participation from week 1 (~92 min/week) through week 7 (~30 min/week). Weekly yoga participation remained relatively stable around ~25-30 min/week from week 7 through week 12.

Self-report yoga participation (i.e., daily yoga log) averaged 56.1 min/week with 48% (n=13/27) averaging ≥60 min/week. There was an increase in weekly yoga participation from week 1 (~49 min/week) through week 3 (~77 min) before declining

back down to week 1 values in week 5 (~49 min/week). From week 5 through week 12, weekly yoga participation remained relatively stable between ~50-60 min/week.

Yoga group participants significantly under-reported yoga participation in week 1 (-45.5±55.9). In weeks 3-12, yoga group participants significantly over-reported yoga participation by 10.0±29.1 min/week at the lowest to 32.6±38.9 min/week at the highest. Figure 4 depicts the trends in weekly yoga participation and compares self-report vs. objective yoga participation. Table 6 describes the reliability of self-report vs. objective yoga participation and presents mean and median differences between self-report and objective yoga participation.

Figure 4. Objective vs. Self-Report Yoga Participation

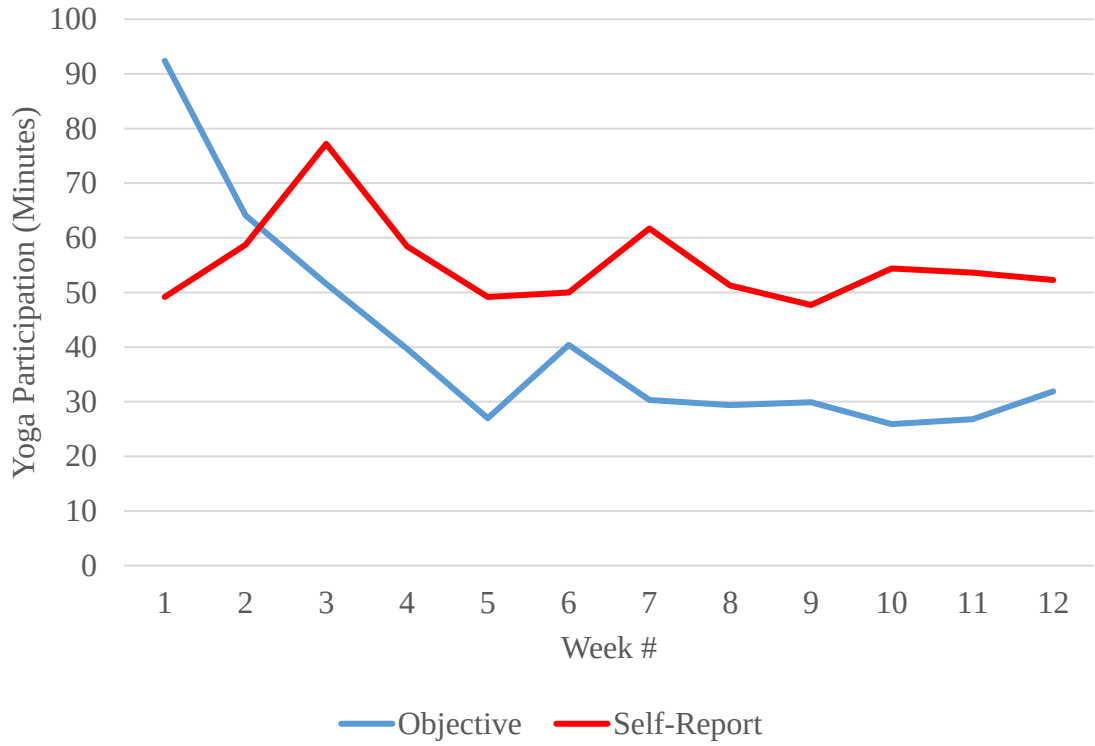


Table 6. Differences Between Self-Report and Objective Yoga Participation					
Week #	**Self-Report (Minutes)**	**Objective (Minutes)**	**Mean Diff (SD)[1]**	**Median Diff[1]**	**P***
1	49.2	92.4	-45.5 (55.9)	-52.0	<0.001
2	58.7	64.1	-12.0 (36.9)	-6.5	0.11
3	77.2	51.6	26.6 (41.6)	28.5	0.003
4	58.4	39.7	19.5 (35.7)	7.2	0.01
5	49.2	27.0	23.1 (25.3)	22.6	<0.001
6	49.9	40.4	10.0 (29.1)	11.5	0.09
7	61.7	30.3	32.6 (38.9)	26.7	<0.001
8	51.3	29.4	22.7 (25.5)	21.1	<0.001
9	47.4	29.9	18.1 (29.7)	6.4	0.005
10	54.4	25.9	29.6 (30.0)	29.2	<0.001
11	53.6	26.8	27.8 (28.8)	30.4	<0.001
12	52.3	31.9	22.5 (29.7)	18.8	0.001
Average	56.1	40.8	---	---	

[1]Self-Report Yoga Min – Objective Yoga Min
*T-Test (Mu0=0)

*Changes in Fatigue and Qo*L

At mid-point (week 7), there were no significant differences in MPN SAF Fatigue, MPN SAF QoL, or NIH Global Health QoL between the yoga group and the control group. At post-intervention (week 12), there were no significant differences in MPN SAF Fatigue and MPN SAF QoL between the yoga group and the control group; however, there was a significant difference in NIH Global Health QoL between the yoga

group and the control group (ES=0.7; p=0.031). Table 7 describes the changes in fatigue and QoL across intervention time points.

Table 7. Changes in Fatigue and QoL

	Yoga Group (n=27)	Control Group (n=21)		
	Mean (SD)	**Mean (SD)**	***d***	**p[1]**
Fatigue				
Fatigue baseline*	5.4±2.3	4.5±2.8	-	-
Fatigue wk 7*	4.6±2.4	3.5±2.3	0.47	0.36
Fatigue wk 12*	4.9±2.6	4.5±1.8	0.18	0.72
QoL				
MPN SAF QoL baseline**	6.2±1.7	6.9±2.0	-	-
MPN SAF QoL wk 7**	7.2±2.6	8.0±2.3	-0.33	0.4
MPN SAF QoL wk 12**	6.4±2.4	7.4±1.2	-0.53	0.2
NIH Global Health QoL baseline***	3.1±0.8	2.6±0.9	-	-
NIH Global Health QoL wk 7***	2.6±0.6	2.2±0.7	0.62	0.14
NIH Global Health QoL wk 12***	2.9±0.8	2.2±0.6	0.7	*0.03*

[1]p-value obtained from ANCOVA using baseline score as covariate

*Fatigue was a single question on the MPN-SAF with a possible score of 0-10; a higher score represents greater fatigue

**MPN SAF QoL was a single question on the MPN-SAF with a possible score of 1-10; a higher score represents greater QoL

***NIH Global Health QoL was a single question on the NIH Global Health Scale with a possible score of 1-5; a lower score represents greater QoL

Note: cohen's d was used for effect sizes

DISCUSSION

The purpose of this study was to examine the efficacy of using online-streamed yoga to improve fatigue and QoL in MPN patients as compared to a wait-list control group. We also examined the feasibility of collecting blood samples and saliva samples from a national sample of MPN Patients. This study builds upon a previous feasibility study conducted by Huberty et al.[25] in which 12-weeks of online-streamed yoga was both feasible and preliminarily effective at improving total symptom burden, fatigue, anxiety, depression, and sleep disturbance. The present study did not find any significant effects of yoga on fatigue when compared to a control group, however, QoL as measured by NIH PROMIS Global Health scale was significantly improved in the yoga group at the post-intervention time point (i.e., week 12) as compared to a control group.

Over the span of six months (i.e., September 2016 to February 2017), we were able to recruit and enroll 62 study participants into the study. Additionally, within this same time period, 260 MPN patients completed the eligibility survey. It is not surprising that we were able to reach our recruitment goal of 60 MPN patients. In our prior feasibility study we were able to enroll 55 MPN patients in just two weeks.[25] There is clearly an interest in complementary approaches among the MPN patient population with an impressive response rate in both our feasibility study as well as the current pilot study.

Of the 260 MPN patients that completed the eligibility survey, 63% (n=164) were ineligible, with 1) currently physically active (n=81), 2) moderate-severe levels of depression (n=61), and 3) currently engage in regular mindful activity (n=43) being the most common reasons for ineligibility. This is similar to our prior feasibility study in which a diagnosis of depression, anxiety, or post-traumatic stress disorder as well as

currently engaging in regular mindful activity were the two most common reasons for ineligibility.[25]

Twenty three percent of participants dropped out of our study, which is comparable to other yoga interventions in cancer patients.[33] In a recent systematic review of yoga interventions for fatigue in cancer patients and survivors, dropout rates ranged between 9% to 41%, with the average dropout rate being ~19% across 10 studies that were included in the review.[33] However, the studies included in this review were in breast cancer patients (i.e., 9/10 studies in the review) and were of in-person yoga interventions as opposed to online, home-based yoga interventions. In health promotion interventions delivered online, dropout rates are ~32% on average according to a recent meta-analysis.[38]

We had fewer dropouts in the current study as compared to our prior feasibility study[25] which had a dropout rate of 31%. Our prior feasibility study informed modifications to the current study which may have contributed to a smaller dropout rate. Participants in the original feasibility study reported wanting more meditative class options. Thus, we added short (i.e., 5-20 min) meditation videos as alternative videos for weeks 3-12.

The blood draw was determined to be feasible based on a priori practicality criteria. More than 70% of study participants completed the blood draw measure at both pre-intervention (i.e., 92.6%) and post-intervention (i.e., 70.4%). The salivary cortisol measure was not determined to be feasible (i.e., not practical) as only 60% of study participants completed this measure at post-intervention, which was a 33% lower completion rate when compared to pre-intervention (i.e., 93.3%). Both the completion

rates for the blood draw and the salivary cortisol measure, however, are higher than what has been demonstrated in another study that aimed to determine the feasibility of collecting saliva, blood, or stool samples in an internet-based cohort of inflammatory bowel disease (IBD) patients.[34] A total of 591 IBD patients were randomly invited to provide either 1) a blood sample through a mobile phlebotomy service, 2) a blood sample through a local physician's office, or 3) a saliva sample via a mailed saliva collection kit. Of the 591 patients that were asked to provide a sample, only 28.9% (n=171) contributed a biospecimen, of which 90 were saliva samples, 47 were blood samples through mobile phlebotomy service, and 34 were blood samples through a physician's office.[34]Although this study was not in cancer patients, it is the only study to the author's knowledge that reported feasibility of collecting both blood and saliva samples in an internet-based study that included a national sample of study participants. Our completion rates for the blood and saliva measures between both pre- and post-intervention are higher than that demonstrated in this cross-sectional study. Despite the salivary cortisol measure being deemed impractical in our study and the completion rate decreasing from pre-intervention (i.e., 93.3%) to post-intervention (i.e., 60%), these completion rates are promising nonetheless. Especially because the salivary cortisol measure was not incentivized. Therefore it is possible that there was a greater drop-off in salivary cortisol completion rate from pre- to post-intervention when compared to the blood draw measure due to lack of incentive. Future studies should consider incentivizing completion of either/or the blood draw and saliva sample group as incentives may improve completion rates.

For the entire 12-week intervention, objective yoga participation averaged ~41 min/week while self-report yoga participation averaged ~56 min/week. Objective yoga

participation saw a steady decrease from week 1 (92.4 min) through week 5 (27.0 min), whereas self-report yoga participation increased steadily from week 1 (49.2 min) through week 3 (77.2 min) before decreasing slightly from week 4 (58.4 min) through week 6 (49.9 min). Interestingly, there was a small spike in yoga participation at mid-intervention for both objective and self-report yoga participation before remaining relatively stable at ~30 min/week for objective yoga participation and ~50 min/week for self-report yoga participation.

It is difficult to know whether this level of discrepancy between self-report and objective yoga participation is typical as most of the literature has focused on the differences between self-report and objectively-measured physical activity (i.e., aerobic activity minutes). It has been demonstrated that self-reported physical activity is typically over-reported when compared to objectively-measured physical activity and that it is potentially due to a social desirability bias (i.e., desire to meet or exceed expectations) or the need for social approval (i.e., approval of a behavior).[35,37] It is certainly possible that MPN patients in the present study over-reported their yoga participation in weeks 3-12 due to a desire to appear more compliant with the prescribed 60 min/week of yoga or to gain approval from us as researchers for their efforts despite objectively participating in less than what they reported.

Due to large, statistically significant differences between self-reported yoga participation and objectively-measured yoga participation across the 12-week intervention (all weeks except weeks 2 and 6), it seems that self-report may not be needed and/or necessary due to the potential for over-reporting. Therefore, future studies involving online yoga may be best served to assess study adherence and fidelity through

an objective measure of yoga participation due to the over-reporting of yoga participation that is apparent with self-report methods. Furthermore, eliminating self-report measures may also reduce participant burden as tracking yoga participation requires weekly or even daily time and energy on behalf of the participant.

There was a significant improvement in NIH PROMIS QoL at post-intervention in the yoga group when compared to the control group. Although this was the only significant finding from the current study, it is important to note that there were non-significant improvements in fatigue (ES=0.18; p=0.724) and MPN SAF QoL (ES=-0.53; p=0.19) from baseline to post-intervention for yoga group participants. Furthermore, moderate effect sizes of -0.53 and 0.7 for MPN SAF QoL and NIH PROMIS QoL, respectively, are promising considering the relatively small sample sizes in both the yoga group (n=27) and control group (n=21). These small sample sizes limited our ability to test effectiveness and could explain why we did not find significant improvements in fatigue and MPN SAF QoL. Additionally, the control group also improved across all three outcomes (i.e., MPN SAF fatigue, MPN SAF QoL, and NIH PROMIS QoL) from pre- to post-intervention, possibly explaining why there were non-significant improvements in fatigue and MPN SAF QoL in the yoga group.

In our previous work, we identified online-streamed yoga as a potential complementary approach that could be recommended by physicians for MPN symptom management.[25] Given the promising effects of yoga demonstrated in our feasibility study (i.e., improvements in total symptom burden, fatigue, depression, anxiety, pain, sleep) and the present pilot study (i.e., improvements in QoL), it seems that this suggestion still

holds merit. However, additional research is warranted to shed further light onto the effects that yoga has on MPN patient symptom burden and QoL.

Our feasibility study demonstrated the potential for yoga to improve fatigue. Although there was a non-significant improvement in fatigue at mid-point and post-intervention in the present study, it is important to note that the online yoga intervention did have a moderate effect on fatigue at mid-point (i.e., week 7) and a small effect at post-intervention (i.e., week 12). Fatigue is the most commonly reported symptom in MPN patients[6] as well as one of the symptoms that is often left unaddressed by current pharmacologic treatment.[17,18] Despite the non-significant improvements in the present study, the moderate effect seen at mid-point is promising and therefore, warrants a further exploration of the effects of yoga on fatigue in a randomized controlled trial with larger sample sizes. Additionally, these trials should explore the effectiveness of yoga on other commonly reported symptoms (e.g., pain, depression, anxiety, sleep disturbance, etc.) in order to determine which symptoms yoga may be most beneficial for.

Limitations

Although online yoga was effective for improving QoL and the blood draw measure was deemed to be feasible, there are a few limitations to note. First, small sample sizes in both the yoga group (n=27) and the control group (n=21) may have limited our ability to test effectiveness due to a lack of power. Future randomized control trials should include larger group sizes. Second, the majority of our sample was female (93.8%), potentially leading to a biased sample. The typical MPN patient population is ~53% female,[36] suggesting that we have a proportionately biased sample towards females. This may simply be due to the nature of our intervention (i.e., yoga) and the self-

selecting process of enrollment that we had in place. Future studies should aim to include a more representative sample of males and females. This could be done by blinding potential study participants to the specific type of intervention (i.e., physical activity vs. yoga). Third, the BMI of our sample is 26.5±5.4 kg/m^2, which is difficult to compare to published MPN patient norms as this data is not readily available. When comparing to the published norms for adults in the US (~26.5 kg/m^2), however, our MPN patients' BMI is very similar.[39] National data on MPN patient characteristics is not currently available, despite this data existing for most other cancer types. A database containing MPN patient characteristics and demographics would be useful for future studies wanting to compare their patient population with population norms. Finally, the outcome measures included in this study were all single-question measures taken from validated questionnaires (i.e., MPN SAF and NIH PROMIS). It is possible that more robust questionnaires addressing multiple components of fatigue and QoL are needed to better detect changes in these outcomes. Although each of these single-item questions were taken from well-validated questionnaires, future studies examining changes in fatigue and QoL could consider including more comprehensive, multiple-item questionnaires to better assess these outcomes. For example, the Quality of Life Scale is a multidimensional QoL measure that has been validated in other chronic illness populations and the Brief Fatigue Inventory is a popular and validated multi-item fatigue scale used in cancer patients.

Conclusions

A 12-week, home-based, online yoga intervention is effective for improving QoL in MPN patients when compared to a wait-list control group and has a moderate, but not statistically significant, effect on fatigue. Additionally, collecting blood samples remotely

in a national sample is feasible (i.e., practical). This study builds upon a prior feasibility study that demonstrated online yoga's feasibility and preliminary effects on MPN patient symptom burden. Collectively, these studies yield positive findings and warrant further research investigating the effects of online yoga for MPN patient symptom burden and QoL. Future randomized controlled trials should include larger sample sizes with a more representative gender distribution. Finally, given the feasibility of remotely collecting blood samples, an exploration of the effects of yoga on blood biomarkers associated with symptom burden in MPN patients is warranted.

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APPENDIX A

IRB APPROVAL LETTER

APPROVAL: EXPEDITED REVIEW

Jennifer Huberty

SNHP: Exercise Science and Health Promotion

Jennifer.Huberty@asu.edu

Dear Jennifer Huberty:

On 5/26/2016 the ASU IRB reviewed the following protocol:

Type of Review:	Initial Study
Title:	A Pilot Study of Online Yoga to Improve Symptom Burden (i.e., Fatigue) and Quality of Life in MPN Patients
Investigator:	Jennifer Huberty
IRB ID:	STUDY00004303
Category of review:	(2)(a) Blood samples from healthy, non-pregnant adults, (4) Noninvasive procedures, (7)(a) Behavioral research
Funding:	Name: Mayo Clinic Scottsdale
Grant Title:	
Grant ID:	
Documents Reviewed	• MPN Yoga_Email for previously interested MPN patients_4-27-16_RE.pdf, Category: Recruitment Materials; • Control Group Welcome Letter, Category: Participant materials (specific directions for them); • Control Group Important Dates , Category: Participant materials (specific directions for them); • Yoga Group Weekly Email Reminders, Category: Recruitment materials/advertisements /verbal scripts/phone scripts; • MPN Yoga_ Informed Consent_Modified_ 5-24-16_RE.pdf, Category: Consent Form; • Yoga Group 4-Week Follow-Up Questionnaire, Category: Measures (Survey

	questions/Interview questions /interview guides/focus group questions); • Pilot study IRB Draft_Modified_5-24-16 RE.docx, Category: IRB Protocol; • Interview Questions, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • MPNYoga_Flyer_NoTrackChanges_5-24-16_RE.pdf, Category: Recruitment Materials; • Control Group Weekly Log, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Yoga Group Post-Intervention Questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Yoga Group important Dates, Category: Participant materials (specific directions for them); • MPN Yoga_Professional Recruitment Blurb_Drs. Huberty&Mesa Bio_NoTrackChanges_5-24-16_RE (1).pdf, Category: Recruitment Materials; • Study Protocol, Category: Other (to reflect anything not captured above); • Mid-Point Questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Yoga Group Daily Log, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Yoga Group Weekly log, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Yoga Group Welcome Letter, Category: Participant materials (specific directions for them); • Control Group 4-Week Follow-Up Questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • MPN Yoga_Social Media & Email Blurbs_NoTrackChanges_5-24-16_RE.pdf, Category: Recruitment Materials;

	• Yoga Modifications Handout, Category: Participant materials (specific directions for them); • Eligibility Questionnaire, Category: Screening forms; • Yoga Prop Alternatives, Category: Participant materials (specific directions for them); • Control Group Post-Intervention Questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions); • Informed Consent for Eligibility Questionnaire_5-17-16_RE.pdf, Category: Consent Form; • Participant Fitbit Instructions, Category: Participant materials (specific directions for them); • Yoga Group Udaya Instructions, Category: Participant materials (specific directions for them); • Baseline Questionnaire, Category: Measures (Survey questions/Interview questions /interview guides/focus group questions);

The IRB approved the protocol from 5/26/2016 to 5/25/2017 inclusive. Three weeks before 5/25/2017 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 5/25/2017 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the "Documents" tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the

INVESTIGATOR MANUAL (HRP-103).

Sincerely,
IRB Administrator
cc: Ryan Eckert
Ryan Eckert
Rachael Nowak
Lauren Martinez
Jennifer Huberty
Lindsay Hand
Maritza Reyes
Linda Larkey
Jennifer Matthews